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KWASHIORKOR—
The Syndrome of Malignant Malnutrition

By RUTH WOODS

Kwashiorkor is an extremely complex form of nutritional deficiency which today presents one of the greatest challenges to modern nutrition science. First discovered in Africa among children under five years of age, but past early infancy, it has since been recognized in many other parts of the world where tropical climates and grossly inadequate eating habits prevail. Tropical diseases such as malaria, intestinal parasites and hookworm infestation are invariably a part of the clinical picture but have been ruled out as primary factors in its etiology. The clinical features of kwashiorkor closely resemble the manifestations of pellagra, beriberi, nutritional edema and nutritional anemias as observed in the United States, Europe, and the Orient. Yet, kwashiorkor is more than a combination of these diseases. It does not respond to the traditional vitamin therapy of these diseases and it presents a clinical picture which distinguishes it from these diseases in numerous respects — i.e., geographical distribution, age-incidence, response to treatment, general course and mortality.

The study of kwashiorkor, more correctly described as malignant malnutrition because of its unusual resistance to treatment, is at present a major activity of the Food and Agriculture Organization of the United Nations. The concerted efforts of a team of international nutrition authorities are being brought to bear on this extraordinary and highly devastating disease and the results of investigation in this field are being anticipated with utmost interest by students of nutrition throughout the world.

This review will present a brief history of kwashiorkor, its clinical features and relation to the more commonly recognized nutritional deficiency diseases, and will discuss the role of various foods and nutritional factors in its prevention and cure as far as these have been determined by current researches.

Historical Background:

Some eighteen years ago, Cicely Williams, a young woman doctor in the Children's Hospital in Accra on the African Gold Coast, reported the occurrence of a hitherto undescribed children's disease of serious consequences (1). The causes of the disease were obviously many and, for the most part, obscure. One fact, however, stood out with clear-cut certainty: all of the children afflicted were subsisting on extremely unbalanced diets

seriously deficient in most of the essential nutrients. Cicely Williams, therefore, described it as a nutritional disease.

In the decade that followed, reports of the finding of a similar condition among young children in other parts of Africa were published by other workers. The disease was noted among the Bantus of Central Africa, in the Belgian Congo, and in Kenya, Uganda and South Africa. Numerous opinions were advanced as to the specific cause of the disease, but it was impossible to trace it to a deficiency of any one specific nutrient or group of nutrients. For a time, it was considered to result, at least in part, from infectious causes as well as from nutritional deficiency.

In the past decade, the nature of the disease has become somewhat clarified. It has been found to occur in adults as well as in children and has been reported in other tropical and semi-tropical areas besides Africa, and recently among members of the white race. Although the condition has many features in common with pellagra, nutritional edema and nutritional anemia it is not merely a composite of these, nor does it respond to the usual vitamin therapy of these diseases.

Nomenclature: This very characteristic, yet somehow undefinable disease, has been described under many names—none entirely accurate. Popularly, it is known by one of the original African tribal names, ***kwashiorkor***, meaning "red boy" (a reference to the characteristic, but not always present feature of skin and hair discoloration). It has also been described as "infantile pellagra", but recent evidence of its occurrence in adults and of factors distinguishing it from classic pellagra make this term incorrect. Because edema is not always present, the disease cannot be accurately termed nutritional edema; the same applies to names such as nutritional hypoproteinemia*, especially when it is realized that protein deficiency occurs in the tissues as well as in the blood and that B complex deficiency is also involved.

As Trowell (2) has concluded:

> "Unfortunately, it is necessary to call the syndrome by a certain name or it will be seldom diagnosed and treated. Such are the limitations of the human mind. The author suggests that the advanced and complete syndrome be called *'the syndrome of malignant malnutrition.'* It is malignant in the sense that it affects many parts of the body. It is malignant in the sense that it produces as much wasting as does a malignant tumor. It is malignant in the sense that it may not be diagnosed easily in the early stages, but only when advanced cachexia** has occurred and when the case can no longer be saved by diet alone, for the patient cannot assimilate it.

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*More accurately hypo-albuminemia, since serum albumin is low, but total plasma protein levels may be normal.

***Ed. Note.* A general lack of nutrition and wasting occurring in the course of a chronic disease.

"The condition should be called a syndrome and not a disease, for it is probably, strictly speaking, not a clinical entity. It is a pattern of disease and of multiple nutritional defects. The strands of the weft are the dominant colors in the pattern: total calories, protein, vitamin B complex; the warp of the pattern has many different strands of an infective nature: helminths, pneumonia, and so on. The pattern produced is confused, but a certain drab monotony is seen in the clinical picture. It is the considered opinion of many clinical workers in the tropics that it is the commonest malnutritional disease of the negro of Central Africa."

Clinical Background in Early Studies:

In the original report on the occurrence of kwashiorkor in children of the Gold Coast Colony, Cicely Williams (1) describes the native tribal customs which, in conjunction with the diet eaten, combine to bring about this syndrome.

Family Customs: Babies are breast fed until the next child is born — a period rarely less than two years. Children may be given occasional breast feeds even then, up to the age of six or more, chiefly as a means of pacification in moments of stress. Lactation is greater among African women, sometimes persisting to some degree in quite old women who may not have had a child in twenty years. Thus, grandmothers, aunts, and other women often will nurse older children on occasion or will adopt an infant whose mother has died in childbirth or soon after. Such foster children generally die early because of the inadequacy of the milk supply. In obtaining a case history when a child is brought to the clinic, it is important, therefore, to learn if the child is motherless or not. This fact, however, is often ignored by the family or even concealed by some tribes who believe that an infant which survives its mother is a bad spirit and should be destroyed.

Most of the babies brought to the clinic for treatment thus present a history of improper feeding. Usually the child has not been breast fed by the mother — due to a subsequent pregnancy while the child was still young, or because the mother was ill or undernourished, or because of death of the mother. Supplementary feeds have consisted of nothing but preparations of corn known as arkasa and kenki.*

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*Arkasa: Soured corn-dough mixed with water to a smooth paste and then finely sieved. More water and salt are added and the mixture boiled for fifteen minutes. Sugar is often added at the end. It forms a rather thick gruel. Arkasa is the only supplemental food given to babies.

Kenki: Corn soaked in water for three days; then stone ground, sprinkled with water and put in a pot covered with plantain leaves and left for three days to sour; then ground smooth, divided in half. One half is put in a pot of boiling water and stirred until thoroughly mixed. Then the pot is taken from the fire and the uncooked half mixed with the cooked half and the whole mixture is then rolled in plaintain leaves or in corn hash and boiled in water for several hours. Kenki is given to older children in addition to arkasa, and forms a major staple of the adult diet.

Adult Diet: The diet of the average adult on the Gold Coast consists mainly of kenki and other bulky carbohydrates — yams, cassava or cocoa-yams (boiled or roasted or beaten into a puree known as a "fu-fu"). This is supplemented with small amounts of dried fish or a stew made of meat, tomato, onions, okra, eggplant or beans, highly seasoned with fiery peppers. Meat of goats, sheep, and chickens is used only in small quantities. Beef is seldom used and only in the towns. Butter is unknown except as obtained on occasion from cans. Fats are provided mainly from palm oil, palm-kernel, cocoa-nut oil and ground nuts. Milk, except as breast milk, is not used. Canned condensed milk is sold in many villages as a luxury item for adults. Welfare workers attempt to encourage the introduction of milk to children's diets. Some eggs are eaten, usually only when hard-boiled. Animal fats are almost entirely lacking in the diet. Fruit is eaten only occasionally and consists of bananas, oranges, pineapples, paw-paws, mangoes and avocados. Tomatoes, eggplant, okra and onions are widely grown and are used in every soup or stew.

Thus it can be seen that even the adult diet is far from nutritionally perfect — lacking chiefly in good quality animal protein, milk and animal fats, and containing excessive amounts of carbohydrate. Thus it may be expected that most babies are born with poor nutritional stores, with respect to many nutrients, and that when the added factors of poor quality breast milk, inadequate supplementary foods, and common tropical infections prevail, nutritional failure—such as is evidenced in kwashiorkor—is inevitable.

Clinical Symptoms of Kwashiorkor: As described by Williams:

> "The early picture is one of a child of about eighteen months old, well nourished but irritable, with slight oedema of the hands and feet, and the skin showing some degree of depigmentation. There suddenly appear on the ankles, on the knees, above the wrists, and on the elbows, some small black patches, first on the extensor surfaces and gradually spreading. These patches appear to consist of the epidermis which has become dark, thickened and crumpled, though it remains soft and pliable. The number and extent of these patches increase. Their distribution and their character remain distinct from the rash that is typical of pellagra. Soon the legs and forearms, knees and elbows, are covered with a sort of crazy pavement of this thickened epidermis. In a few days as the older patches mature, they strip off very readily, leaving a pink, raw surface exposed underneath. The oedema subsides at this stage. The patches of desquamation progress up the thigh and may become severe on the buttocks. Very small patches may also be seen on the face, back, and elsewhere.
>
> "The appearance of the skin condition at this stage is striking. There is the dark or reddish brown of the unaffected skin, the black patches of crumpled and thickened epidermis, and the raw areas where these have peeled off.
>
> "It may be noted that the blackened patches on the skin appear first where

there is any focus of irritation or pressure. The areas round the ankles, below the knees, and above the wrists are probably determined by the strings of beads invariably worn in these positions. Over the knees, elbows, and buttocks are normal pressure points in a child who is beginning to crawl.

"The skin at the corners of the mouth and eyes also begins to peel off, leaving raw areas. There is photophobia, but no eversion of the eyelid as described in the A and B deficiency of Sierra Leone.

"By this time the child is in a miserable condition with sores on the mucous membranes, and perhaps a corneal ulcer. Conjunctivitis has not been marked; there has been no dryness of the cornea nor any condition resembling Bitot's spots. Diarrhoea is persistent, especially in the later stages. The child is extremely irritable, and may die in a few days if it is not treated. It appears that unless the diet is changed before the skin condition is fully developed it is impossible to save the child's life."

From the early observations of Williams, the only characteristic anatomic abnormality observed post-mortem was the development of a pale, fatty liver in all cases and occasional kidney degeneration.*

Treatment: Some success in arresting the progress of the disease and even in affecting cures was achieved through the use of a full and varied diet (containing chiefly canned milk, malt, cod-liver oil, yeast, fruit, eggs, iron, butter, meat juice) plus medication for the lesions of the skin, eyes, and mouth. This diet was followed only when the child was hospitalized; when removed to the home most children were given only the corn cereals arkasa and kenki and soon relapsed, with fatal consequences. In a typical case cited, the mother admitted, after the child's death, not following diet instructions, adding that she had given the child milk only once and never again because it made the child's mouth messy.

Williams concluded:

"It has been impossible to conduct a scientific investigation into the cause or to make controlled experiments into the nature of the cure. But my general impression is that the most important elements in the treatment adopted were cod-liver oil and a good brand of tinned milk. The cod liver oil given to out-patients seemed to delay the onset of the fulminating stage; but it was only with in-patients, for whom an adequate supply of good milk could be assured, that a cure was established.

"The authorities might well actively encourage the use of milk. Merchants should be able to import reputable brands of milk, duty free if possible. The agriculturists will bestow an inestimable blessing when they will introduce a milking strain of goats to cross with the native goats. The educationalists might well devote time to teaching their pupils how to obtain milk, butter and cheese from these animals, and include information on hygiene and feeding in the educational syllabus."

**Ed. Note.* Highly suggestive of choline deficiency or of lack of other dietary lipotropic factors, such as methionine, inositol, lipocaic.

Modern Concepts of the Nature of Kwashiorkor:

Since the early studies of Williams, kwashiorkor has been recognized in many parts of Africa and other tropical areas throughout the world and studied by nearly a hundred different investigators. Figure 1, taken from Trowell (3) shows the geographical distribution of malignant malnutrition.

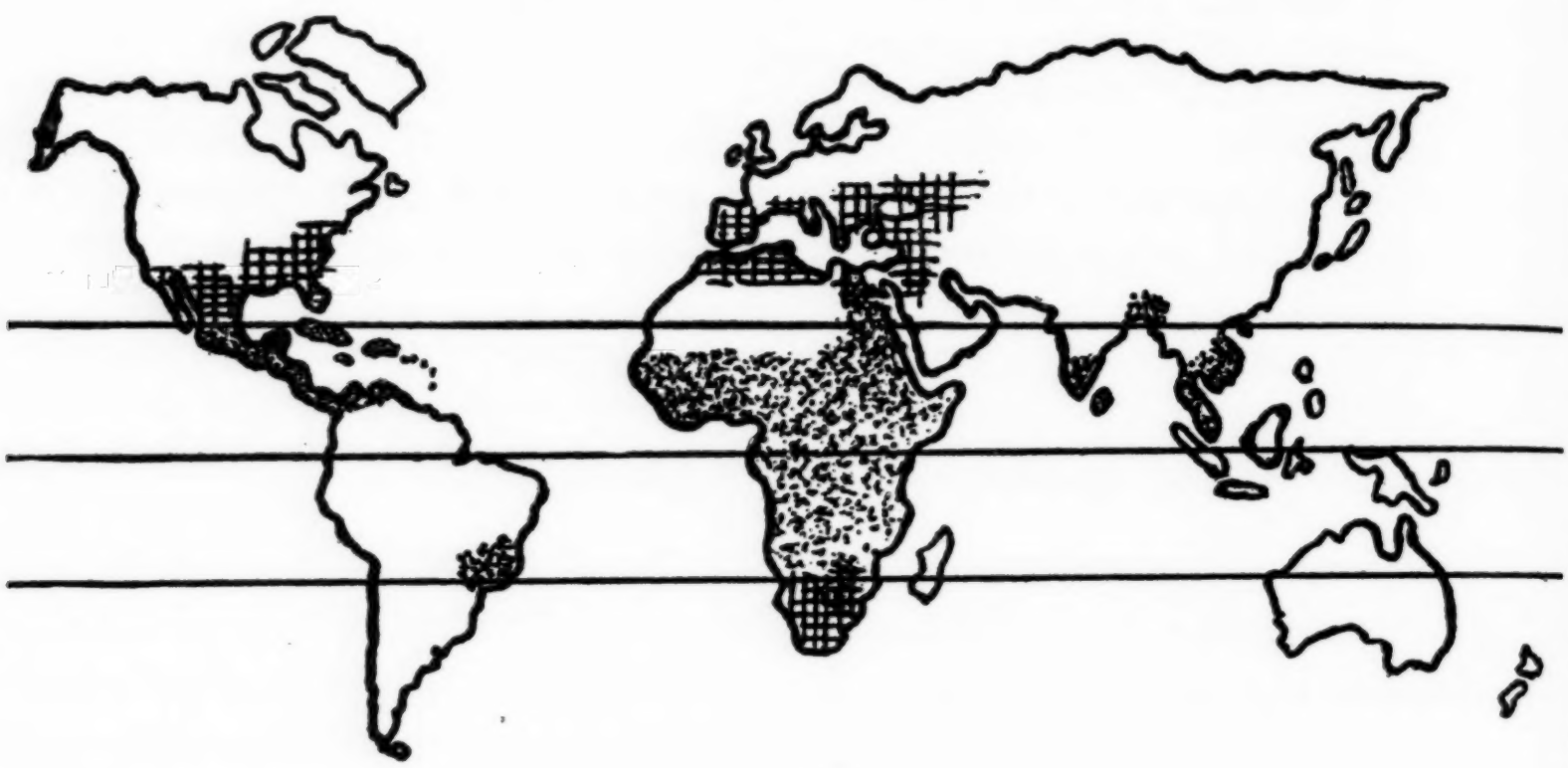

FIG. 1.—Distribution of Malignant Malnutrition (Stippled) and Classical Pellagra (Hatched).

It will be seen that the syndrome is limited almost entirely to the tropics. Its absence in the United States and in the East Indies and the Pacific Islands is extremely thought-provoking inasmuch as there is a great deal of pellagra in the United States and a marked prevalence of tropical disease in the latter area. In recent years it has been shown that kwashiorkor occurs in southern India (4, 5, 6), in Brazil, Central America, and the West Indies. Except for its occurrence in part of India and other small areas in Asia (Fig. 1), kwashiorkor is strikingly absent in Asia. One is led to speculate as to the probable protective role of rice — the major dietary staple in Asia, as contrasted to that of maize, the chief staple in areas where both pellagra and kwashiorkor are prevalent. Although both rice and maize serve chiefly as sources of carbohydrate, rice contributes a fair amount of good quality (though not complete) protein, whereas the proteins of maize (chiefly zein) are known to be grossly inadequate.

There has been no published report of kwashiorkor among the well-known Masai tribe in Africa. This tribe subsists largely on meat, and has a reputation for great strength, vigor and warlike activity, in contrast to a neighboring tribe — almost exclusively vegetarians — who are considerably

less vigorous. The Masai adults also reach a stature of 6 feet or more, whereas their close-by neighbors are generally much shorter in height.

Relation to Pellagra: Kwashiorkor has many symptoms in common with pellagra, but it also differs from pellagra in many important respects. There has been considerable difference of opinion as to the relationship of these two conditions to each other. For one, the geographical distribution of the two diseases differs. Secondly, classic pellagra occurs more usually in adults; kwashiorkor, in children. Gillman and Gillman (7) believe kwashiorkor to be a form of infantile pellagra. They found, however, that it failed to respond to vitamin therapy, becoming, in fact, severely aggravated by such treatment and usually ending fatally. They reported that the condition could be cured by the administration of powdered hog stomach, (and, to a lesser extent, by liver extract) but this has not been generally confirmed by other workers. Adult pellagra responds favorably to multi-vitamin therapy, particularly to nicotinic acid. As the Gillmans and others have found, "infantile pellagra" or kwashiorkor does not respond to such treatment — it requires, in addition, a good, general diet, particularly rich in animal protein and the treatment of all co-existing infections.

The Skin Manifestations: In children, marked changes are seen in the color of the skin and hair. The hair changes usually are the first to appear and consist of changes in both color and texture. The normal jet-black, wiry curls become reddish or even straw colored, softer and straighter. In severe cases, baldness may ensue. The normal rich dark skin becomes pale, varying in color through all shades of light and dark coffee or, in mild cases, exhibiting a reddish, chocolate tint. A characteristic dermatosis is almost always present and has been described as "mosaic" or "crazy pavement" skin. This consists of thickened, darkened patches of skin (occurring even on a skin which has become generally pale) which affect primarily the sites of irritation and pressure — the shins, thighs, and back, and, in young children, the folds of arms, legs and groin. Unlike the dermatosis of pellagra which it somewhat resembles, the dermatosis of kwashiorkor is not aggravated by exposure to sunlight. Treatment with nicotinic acid, however, often causes desquamation of these hardened patches with subsequent formation of healthy new skin beneath (2). Other manifestations of the kwashiorkor syndrome remain unaffected by nicotinic acid therapy.

The Liver Picture in Kwashiorkor: As noted by Williams and all other investigators since, a major aspect of kwashiorkor is the development of an enlarged, fatty liver. This occurs almost universally in the course of the dis-

ease, whether or not the characteristic pattern of "crazy-pavement dermatosis" is present. The condition, if untreated, generally develops into varying degrees of cirrhosis of the liver. Trowell (3) has reported on the efficacy of various dietary supplements in removing excess fat from the liver (determined by biopsy examinations) and in effecting clinical improvement in a small group of children suffering from malignant malnutrition. (Table 1).

TABLE 1. Lipotropic Action in Malignant Malnutrition in Children (3)

Cases	Daily Supplements	Lipotropic Action	Clinical Results
2	None*	Slow improvement	2 very slowly improved
3	¼-lb. meat	Much improvement	3 improved
3	¼-lb. liver	Much improvement	3 improved
3	1 pint milk**	Much improvement	3 improved
4	5 gm. hog's stomach	Doubtful improvement	2 improved; 2 died
2	2 gm. choline	Very slight improvement	doubtful response

*Ordinary hospital diet of ¾ pint milk, one ounce meat and cooked plaintains *ad lib.* Other cases received this basic diet, plus the stated supplements.
***i.e.* Imperial pint, equivalent to 20 oz. as compared to U. S. pint of 16 oz.

Although it is difficult to draw a conclusion from such a small series of cases, it would seem that despite the acknowledged lipotropic activities of hog stomach and choline, some additional factor — probably protein — is required to achieve success in the treatment of kwashiorkor with respect to the improvement of both the liver and general clinical condition. In pointing out the obvious value of all forms of animal protein, Trowell (3) states: "If one may hazard any opinion on so small a series, one would suggest that (of the animal proteins) milk is the best." This was also the belief expressed in the original studies of Cicely Williams (1) and, as recently as January of this year, by Sinclair (8).

The Blood Protein Picture: The serum proteins in all cases and in all countries reporting kwashiorkor or malignant malnutrition are always outside of normal ranges. There is a marked drop, in both children and adults, of the serum albumin fraction and often an unexplained rise above normal in the serum globulin levels. The abnormal blood protein picture is usually accompanied by marked edema, especially in the advanced cases in children. The edema closely resembles the type observed in acute nephritis; although kidney function tests indicate normal activity of these organs, there is little or no albumin in the urine, and autopsy findings reveal no evidence of kidney disease. The edema is, therefore, of nutritional origin resulting primarily from inadequate intake of dietary proteins (9). The edema is

often so pronounced as to actually mask the severe loss of weight which accompanies the kwashiorkor syndrome. In those cases where the edema has been found to respond to treatment, patients exhibit a marked "weight" loss due solely to the loss of excess water.

The Anemia of Kwashiorkor: Many types of mild anemia have been found to be associated with the syndrome of malignant malnutrition and there has been some difference of opinion among authorities as to the interpretation and significance of the various findings. Much of the anemia in the Uganda and elsewhere may be traced to hookworm and malarial infection; some types respond to iron or liver therapy; other forms, thought to be "deficiency" anemias, failed to respond to any type of treatment — liver extract, folic acid, hog stomach — until it was pointed out (3, 10) that the so-called "macrocytic anemia" was actually not a sign of deficiency but a phase of slow, chronic blood *regeneration* characterized by the appearance of larger-than-normal blood cells. Treatment of the infections with quinine and subsequent provision of a high protein diet eventually cured the anemia. The occurrence of a mild normocytic anemia in malignant malnutrition in South Africa where there is no tropical disease, however, has been studied by Altmann and Murray (11). In their cases, it appeared that the essential anemia of kwashiorkor reflects a protein deficiency, best responses being obtained on a milk diet.

In view of the lack of response to iron and folic acid and the obvious relationship to protein deficiency, particularly of animal protein, it is intriguing to speculate on the probable role of vitamin B_{12} in kwashiorkor. It may be possible that this vitamin may elicit a response not only with respect to the anemia of this syndrome, but in the general picture of malignant malnutrition. This may be because numerous functions other than those involving hematopoiesis have been attributed to vitamin B_{12} (12) including a probable effect in stimulating both appetite and growth (13).

Other Symptoms: Scott Brown and Trowell (14) described radiological changes in the intestines of children and adults with kwashiorkor. In the small intestine there was segmentation, smoothing of the intestinal folds, decreased bowel tone, and distention of the colon with gas. This picture has been described as the "deficiency bowel pattern" and is similar to the condition found in sprue and in celiac disease.

Lesions of the pancreas in kwashiorkor have also been described by a number of workers including Davies (15) in Kampala in Africa, and Waterlow (16) in the British West Indies, the latter in connection with a related syndrome termed "fatty liver disease of infants."

Other Syndromes of Malnutrition Related to Kwashiorkor:

The term "kwashiorkor" or "malignant malnutrition" refers to the complex dietary deficiency syndrome as seen primarily in Africa. Even in Africa, however, the syndrome exists in many forms and the various disturbances described may not be universally present. In South Africa, for example, where tropical disease is rare, this factor does not enter into the picture of kwashiorkor, and the syndrome, as described by the Gillmans (17, 18, 19) is perhaps the closest to the uncomplicated, pure nutritional deficiency. Again, even in Africa, the characteristic skin lesions and discoloration are not always present, depending on the region in which the disease occurs.

The nutritional disturbance described exhaustively by Waterlow (16) as "fatty liver disease of babies" in the British West Indies (Trinidad, British Guiana, and Jamaica) is undoubtedly either another form of, or very closely related to, African kwashiorkor. The disease in these so-called "sugar-babies" is characterized chiefly by fatty degeneration of the liver; skin lesions are minor or absent, and the relation to pellagra is considered very remote. Here, too, best responses were obtained with milk, while lipotropic agents (choline, methionine, inositol) and vitamins proved relatively ineffective. The diet of West Indian babies, like that in Africa, is excessively high in carbohydrates (hence, the name "sugar babies") and low in proteins, except for very small amounts of milk, which food is completely absent from the diet of African babies after weaning.

The wasting disease attacking European babies in Europe and described by early German pediatricians (20, 21, 22) as "mehlnährschaden" (flour-feeding injury") is now believed to be the European counterpart of "sugar babies" in the West Indies and African kwashiorkor. In this disease, excessive carbohydrates were fed and edema and fatty liver were characteristic findings. The fatty liver of mehlnährschadung has been described as more severe than that found in any other type of infantile malnutrition (21, 22).

Conclusion:

Within the last five or six years, and particularly at present, clinical studies on malignant malnutrition and the many variations of this disorder which are becoming apparent throughout widely-scattered areas of the world have been conducted by an increasing number of investigators. It is impossible in the limited space of this review to adequately describe all of the work that has been done and the many invaluable contributions which have been made in connection with this catastrophic nutritional failure.

To date, a small degree of progress has been made in the treatment of malignant malnutrition. The outstanding feature of both the disease and its therapy is the extraordinary resistance to therapy with individual nutrients, whether they be vitamins, lipotropic substances, liver extract, or protein concentrates. Only on a diet of complete foods, preferably of animal protein origin, has any degree of remission been possible in the treatment of malignant malnutrition. There have been many speculations as to the reasons for this, but as yet no satisfactory explanation. In most cases studied, the disturbance has proceeded to the stage where physiological impairment of the liver and digestive tract is so severe as to interfere with the utilization of foods and nutrients when they are finally provided. It may be, as one authority (23) pointed out, that protein deficiency may interfere with the formation of enzymes essential to the utilization of foods, thus explaining both the lack of response to various supplements and the favorable effects of milk. In commenting on this, Trowell has stated:

> "I have always considered this to be a very suggestive point and it may explain why advanced cases fair so poorly on an indifferent native diet containing rather large pellets of potatoes and so forth in the intestine, but benefit so much from milk. The latter and possibly also finely-milled cereals can be tackled by even small amounts of pancreatic and intestinal enzymes, which are unable to tackle a large piece of potato or meat.
>
> "Certainly if one of the undigested pellets of carbohydrate is obtained from the stool and tested with iodine, digestion can be seen to have been fairly good on the surface of the pellet, but it has not started in the interior of the mass."

While much remains to be clarified in the understanding and treatment of malignant malnutrition, considerable progress already has been made by existing researches. The mortality in kwashiorkor, reported by early workers to range from 60% to 90%, has been reduced to less than 10% in the Uganda — to cite one example. The nature of the dietary treatment is known, at least empirically — a liberal diet of small, frequent meals including milk, meat, brown bread, liver, eggs, fish. The major concern is to provide natural foods, particularly those high in animal protein and to treat all concommitant infections which may interfere with health and normal nutrition. It is not too much to expect that the gaining momentum of current and future research will before long arrive at the ultimate specific causes and treatment of this distressing nutritional syndrome.

EDITOR'S NOTE: *The subject of malnutrition in Africa has been exhaustively reviewed in the excellent monograph "Perspective in Human Malnutrition," by J. Gillman and T. Gillman (Grune & Stratton, N. Y.) which appeared just as this issue was sent to press. Because of its relation to the subject matter of this review, this book will be discussed in the forthcoming issue of* BORDEN'S REVIEW OF NUTRITION RESEARCH.

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